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Endocrine Dysfunction and Slipped Capital Femoral Epiphysis[1]

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Five patients with concomitant endocrinopathy and slipped capital femoral epiphysis were studied in detail. One had diabetes and hypothyroidism, one had hypothyroidism, one had hypergonadotropic hypogonadism and two had a craniopharyngioma (one of whom had severe panhypopituitarism post-operatively). An additional seven patients with cranio-pharyngioma revealed marked delay in closure of epiphyses and an additional undiagnosed case of slipped capital femoral epiphysis. Of the six patients with slipped capital femoral epiphysis, three had bilateral and three unilateral involvement. Of the five patients undergoing surgical stabilization, there was significant delay of epiphyseodesis, prompting us to recommend concomitant bone grafting. Histological examination of the femoral head from a three year old child with panhypopituitarism showed marked irregularity of the growth plate and loss of columnar integrity, which may be a predisposing factor to slipping in older children with endocrinopathies. The effects of various hormones on the physis are specifically discussed, especially as they relate to the possible etiology of slipped capital femoral epiphysis.

The possibility that generalized or specific endocrine or metabolic abnormalities cause, or at least predispose, a child to slipped capital femoral epiphysis remains controversial and largely unanswered. Large case series usually do not mention patients with specific endocrinopathies, but rather suggest that the somatotypes associated with slipped capital femoral epiphysis have mild hormonal imbalance, referring to these patients as "Frolich-type" [1]. Since the skeletal entity manifests in relation to the physiologic growth spurt of adolescence, many authors have proposed, without substantiating data, that it is caused by an endocrine disturbance [1–7]. Strange [8] suggested that a major causal factor was quantitative imbalance between growth hormone and sex hormone(s). Yet specific analyses of growth hormone levels in patients with slipped capital femoral epiphysis have not shown significant abnormalities [9], nor is there any evidence, using prevailing analytic methods, that hormonal imbalance exists in the majority of affected children.

In contrast to this lack of evidence of generalized hormonal dysfunction, specific endocrine disorders in patients with slipped capital femoral epiphysis have been described with increasing frequency [4,7,10–25]. Further, there are recent descriptions of slipped capital femoral epiphysis following administration of growth hormone to patients with short stature secondary to hypopituitarism [2,6]. Experimentally both Harris [3] and Morscher [26,27] suggested that gonadotrophins might affect the susceptibility of the physis to shear stress, although none of these studies specifically assessed the capital femur.

In order to create awareness of possible concomitant endocrine dysfunction in patients with slipped capital femoral epiphysis, and the probable cause/effect rela-

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tionship, we will present several patients with documented endocrine disorders and unilateral or bilateral slipped capital femoral epiphysis; the histology of the proximal femur in a three year old with panhypopituitarism, since the alterations of the growth plate suggest a mechanism contributing to slipped epiphysis in older children with similar endocrinopathy; and, an extensive review of the effects of various hormones on skeletal growth to advance a coherent picture of normal and abnormal hormonal/skeletal dynamics, especially as they may relate to the etiology of slipped capital femoral epiphysis.

CASE MATERIAL

Five cases with concomitant endocrinopathy and slipped capital femoral epiphysis were studied in detail:

Case 1: This white male, born in 1959, was in apparent good health until 1963, when the abrupt onset of ketoacidosis led to the diagnosis of diabetes. He has been treated with insulin since. In 1972, he was referred for evaluation of short stature that had been increasingly evident since 1969. At that time he had a chronological age of 12½ years, a bone age of 10 years and a height age of 8½ years (51 inches). Evaluation revealed hypothyroidism, probably due to a previous thyroiditis, with studies showing: thyroxin (T4)-I, 1.2 ug/100 ml (N 3–6), T-3 uptake 116% (N 93–107), antithyroglobulin titer 1:250 (markedly positive for thyroid antibodies) and negative complement fixation, normal serum calcium and phosphate, and normal serum cortisol. He was started on thyroid replacement therapy and two months later began to complain of bilateral thigh pain. Roentgenography revealed bilateral slipped capital femoral epiphyses (Fig. 1). He underwent bilateral Knowles pinning with all pins crossing the physes into the capital femoral ossification centers (Fig. 2). Core biopsies of the capital femoral physes showed disruption of the normal physeal cytoarchitecture similar to that described by others [5,28]. Biopsies of the greater trochanteric physes showed normal cytoarchitecture (compared to normal and other patients with slipped capital femoral epiphyses; Ogden and Southwick, unpublished data). In August, 1974 (two years post-pinning), he finally showed growth plate closure on the left side. During that time the femoral neck (metaphysis) had elongated approximately two millimeters, but the pins were still within the ossification center. In contrast, the right capital femoral physis was still functioning and growth had been sufficient to cause the ossification center to extend beyond the limits of the pins (Fig. 3). Growth hormone levels (L-dopa stimulation) in August, 1974, showed a normal response over several hours, with a peak level of fifteen nanograms per milliliter at one hour. Serum cortisol levels were normal. He was beginning to exhibit normal pubertal development and better longitudinal growth, attaining the twenty-fifth percentile for height. In July, 1975, three years after pinning, the right side finally began to demonstrate physiological epiphyseodesis (medially). There was no further neck growth from August, 1974, and the pins were removed. During this admission ACTH stimulation revealed normal adrenal function. His most recent follow-up (January, 1976) shows completion of physiological epiphyseodesis. He is currently asymptomatic.

Case 2: This white male, born in 1956, was evaluated in 1967 for short stature, headaches and visual field loss. For approximately four years a practitioner had been giving him testosterone injections, which had resulted in precocious puberty. Diagnostic evaluation revealed a large craniopharyngioma. Abdominal film studies showed normal proximal femurs. In April, 1967, he underwent craniotomy for resection of the tumor. His postoperative course was complex. He was comatose for

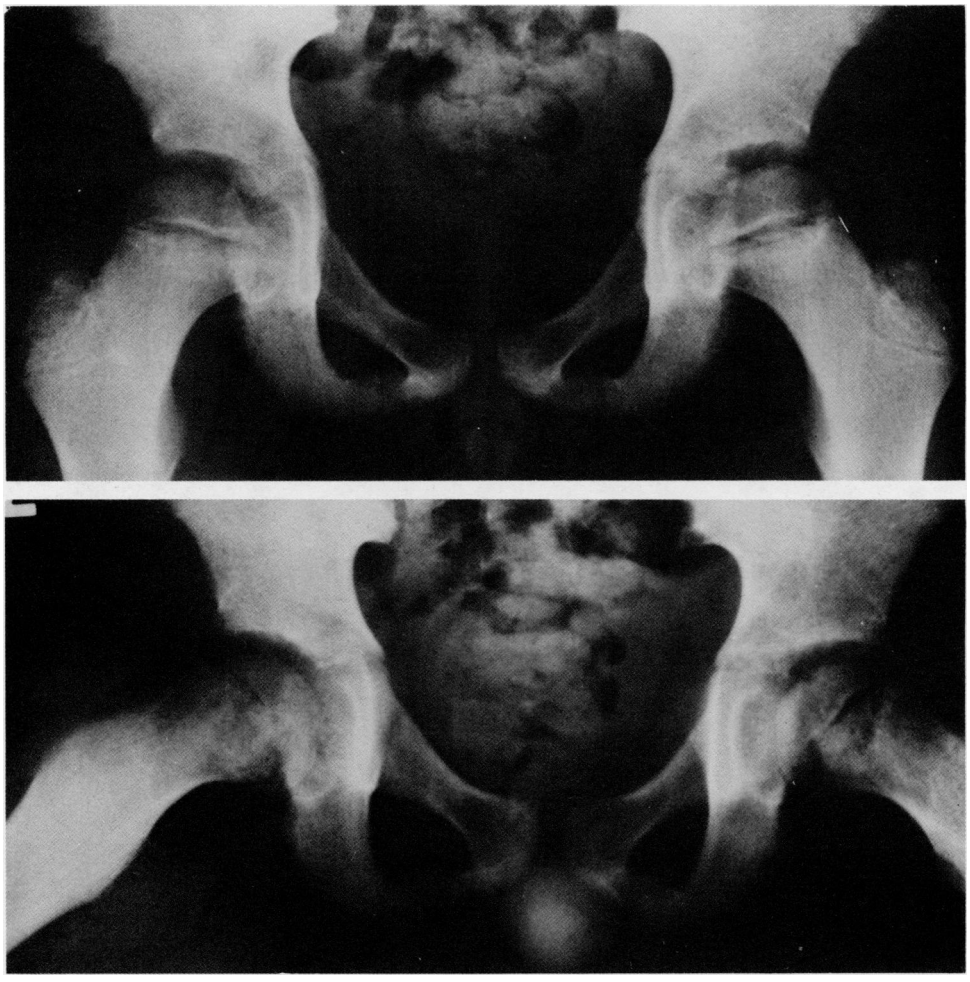

FIG. 1A and 1B. Case 1: Anteroposterior and lateral roentgenograms at age twelve and a half, two months after thyroid replacement therapy was started. Note minimal evidence of slipping in the anteroposterior view, but bilateral slipped epiphyses in the lateral view.

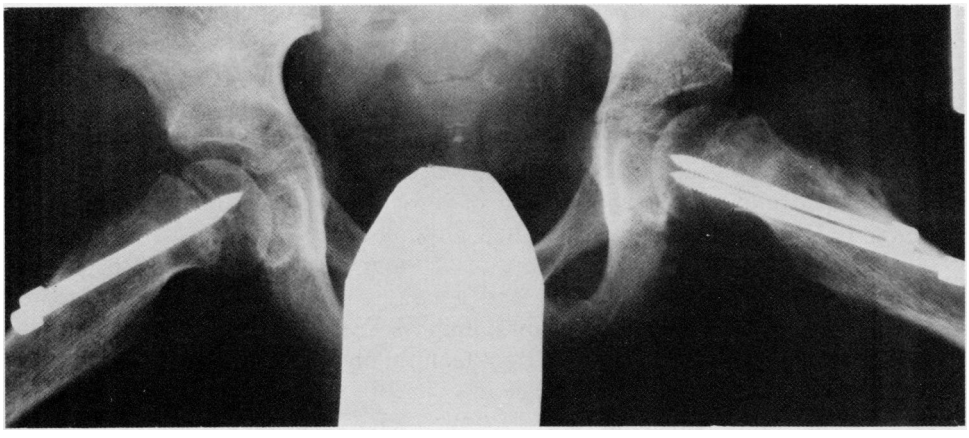

FIG. 2. Case 1: Lateral view immediately after bilateral Knowles pin fixation of each hip. The pins cross the physes into the ossification centers.

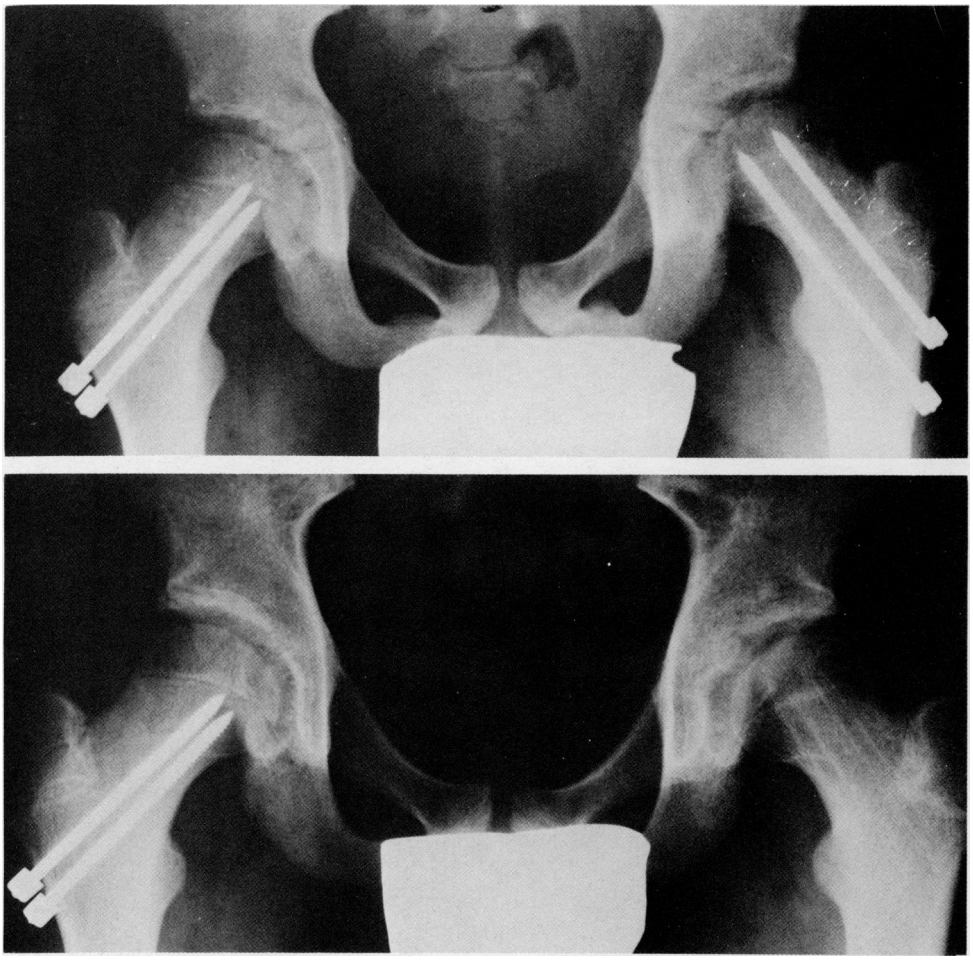

FIG. 3A and 3B. Case 1: A. Anteroposterior roentgenogram two years after surgery. Note closure of the growth plate on the left. However, the right physis continued to function and caused further elongation of the neck, so that only one pin crossed the physis. B. Anteroposterior roentgenogram two and a half years post-hip pinning. Further neck growth occurred and neither pin crossed the physis. The medial portion of the physis has commenced closure.

nine months, and developed panhypopituitarism, with diabetes insipidus, hypothyroidism, hypoadrenalism and severe electrolyte imbalance, hydrocephalus requiring shunting and a severe seizure disorder. In October, 1967 (six months post-op), a pelvic film for evaluation of appendicitis showed bilateral slipped capital femoral epiphyses and he underwent fixation with screws (Fig. 4). He eventually recovered from the coma but was confined to bed and wheelchair. In March, 1969, both physes were still open and there was evidence of loosening around the right screw. In October, 1971, the left side demonstrated physiologic epiphyseodesis. In January, 1972, the right side showed a coxa vara of 95° and still had not fused the physis. Despite the use of steroids for four and a half years, there was no evidence of avascular necrosis of the capital femoral epiphyses. However, the bone was quite osteoporotic. In November, 1972, the right femoral physis finally closed. He remains confined to a wheelchair.

Case 3: This white female, born in 1960, was referred in 1972 from the pediatric endocrinology clinic, where she was being evaluated for short stature and growth

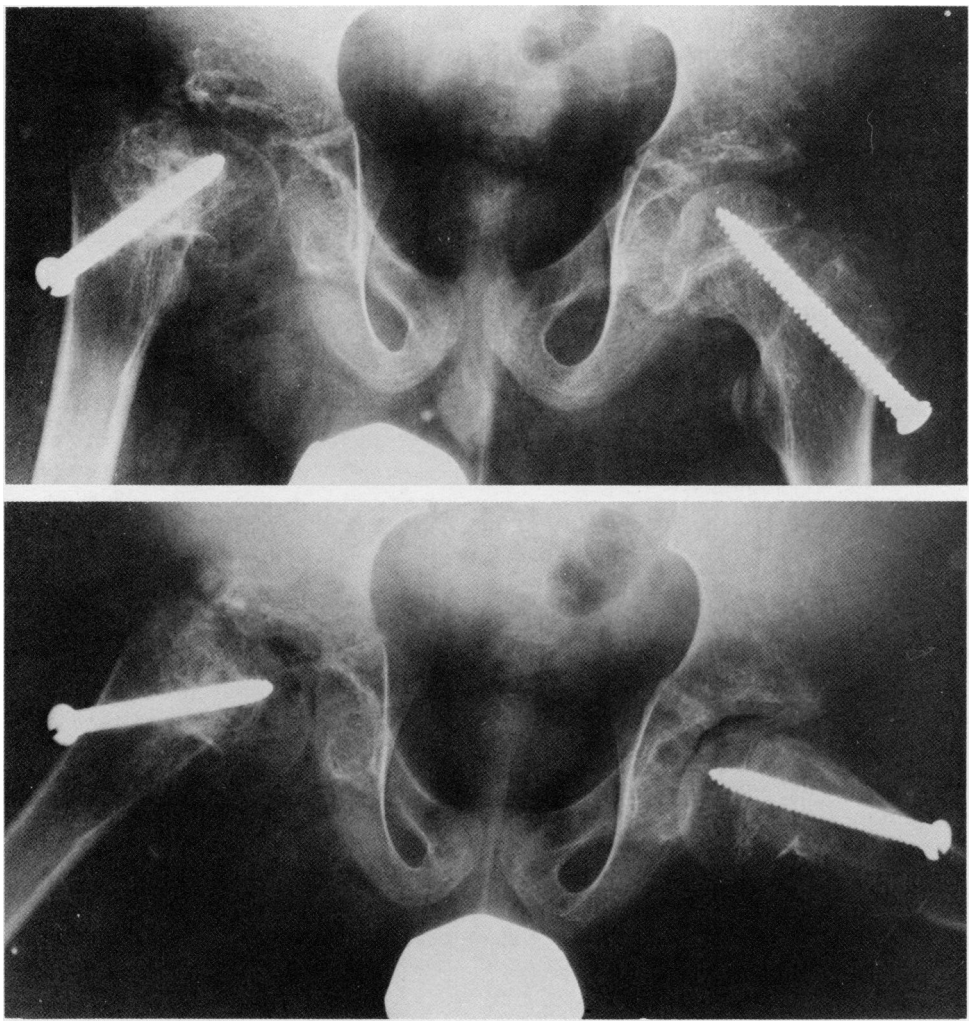

FIG. 4A and 4B. Case 2: Anteroposterior and lateral roentgenograms taken following surgery, demonstrating the severe right-sided and moderate left-sided slipped capital femoral epiphyses. Both were fixed with wood screws. The bones are extremely osteoporotic secondary to the comatose state, bed rest, and multiple metabolic disorders.

retardation (less than third percentile). She was developing secondary sexual characteristics, but had not commenced menstrual flow. Laboratory studies showed normal fasting blood sugar, glucose tolerance test, 17-keto- and hydroxysteroids, growth hormone and urinary estogens. Serum cholesterol was elevated and all thyroid function tests were abnormally low. A diagnosis of hypothyroidism was made. She also had a ten month history of right thigh and knee pain. Roentgenographic examination showed moderate right and minimal left slipped capital femoral epiphyses. She underwent bilateral Knowles pinning. She was started on thyroid replacement therapy. Follow-up radiographs showed an initial widening of the physes (probably in response to the thyroid replacement therapy), followed by narrowing and epiphyseodesis in ten months on the right and eleven months on the left. One year after surgery the pins were removed. She has continued to do well on thyroid replacement and is now fifteen years old, with no evidence of hip symptoms.

Case 4: This white male, born in 1955, was evaluated in 1965 for headaches,

diplopia and short stature, revealing a craniopharyngioma that was surgically removed. Immediate post-operative complications were diabetes insipidus, hypothyroidism and continuous seizures, as well as a transient quadriplegia. He was treated with steroids and thyroid replacement and underwent a growth spurt from the third to fiftieth percentile. In 1970 (age 14), he began to complain of right thigh pain and roentgenograms showed a mild slipped capital femoral epiphysis, which was fixed in situ with Knowles pins. The left hip was asymptomatic and radiologically normal. Both physes closed within fifteen months after surgery. He currently has no hip symptoms.

Case 5: This white female, born in 1959, had a right inguinal hernia repair at three months of age. An operative finding was an infarcted right ovary in the hernia sac. The ovary and tube were placed in the abdomen prior to herniorrhapy. She had a wound infection post-operatively. At age eleven years (1970) she had a seven day menarche but had no further menstrual flow. In 1974, she was given progesterone, but had no breakthrough bleeding. In 1975 (fifteen and a half years), she experienced right hip pain and roentgenograms revealed a severe slipped capital femoral epiphysis. The physes of both the right and left hips were narrowed and obviously beginning physiologic epiphyseodesis. She was treated with a biplane subtrochanteric osteotomy. Physical examination showed no true breast tissue and sparse pubic and axillary hair. Her bone age was 13.5 years. Buccal smear (Barr bodies) was normal for a female (thus ruling out Turner's syndrome). Thyroid indices were normal. Urinary estrogens were 5 mcg/24 hours (lower limit of pre-ovulatory female). LH and FSH were, respectively, 125 and 199 mIU/ml (elevated levels). Provera stimulation failed to induce bleeding. Anti-ovarian antibodies were negative. A diagnosis of hypergonadotrophic hypogonadism (hypoestrogenic state) was made, but it was not definite whether this was primary, due to gonadal agenesis, or secondary, due to an autoimmune oophoritis (possibly related to the ovarian infarction noted as an infant). Four months after surgery a trial of premarin and provera resulted in regular menstrual flow. Nine months after surgery the fixation plate was removed. Both physes had completely closed. The operated side showed some cartilage space narrowing, but this has returned to the pre-operative width on her latest visit (December, 1975).

Correlative Studies: Because of the involvement of several patients with craniopharyngioma (both in this series and the literature), all patients with a diagnosis of craniopharyngioma seen at Yale-New Haven Hospital between 1950 and 1975 were reviewed. Sixteen such patients were initially found. Five patients were deleted because of adult onset of the tumor, lack of endocrine dysfunction and absence of hip pain (three had abdominal films showing normal femoral heads). Four patients were deleted because they were less than ten years of age (two died post-operatively, while two are still alive and are being followed into adolescence). Seven patients with childhood onset of craniopharyngioma were finally selected. They are summarized in Table 1. One patient had a unilateral slipped capital femoral epiphysis, but died consequent to intracranial surgery. The other six patients had no evidence of slipped epiphyses, although several had significantly delayed physiological epiphyseodesis.

A three year old girl with panhypopituitarism who had been followed from birth died of metabolic encephalopathy. Her height and weight had always been below the third percentile. The proximal femur was approximately half normal size (compared to similar-aged specimens; Ogden, unpublished data), but did show development of the capital femoral ossification center (Fig. 5). Microscopic examination showed irregularly decreased cell column length, loss of columnation and greater interstitial

TABLE 1
Additional Patients With Craniopharyngioma

Case	Sex	Age[a]	Height[b]	Weight[c]	Treatment	Thyroid Function	Gonadal Development	Hips/Comments
6	M	16–26	N	N	Craniotomy Radiation	Normal	Normal	Epiphyseodesis[d], 20 y.
7	M	9–26	S	T	Observation	Hypothyroid	Hypogonadal	Epiphyses open, 26 y.
8	M	11–16	S	T	Craniotomy	Hypothyroid	Hypogonadal	No slip noted, 16 y.; lost to further follow-up.
9	F	11–24	N	N	Observation	Normal	Delayed	Epiphyseodesis, 21 y.
10	M	12–19	S	T	Craniotomy	Hypothyroid	Hypogonadal	Epiphyses open, 19 y. (bone age, 14½ y.).
11	M	16–31	S	O	Observation	Hypothyroid	Hypogonadal	Testosterone from age 17; fx. femur 27 y., both epiphyses still open; death 31 y. (no autopsy).
12	M	12–24	S	O	Craniotomy	Hypothyroid	Hypogonadal	Right SCFE; normal left. Death after craniotomy (no autopsy).

[a]Ages patient followed at Yale

[b]N—Normal height; S—Less than 3rd percentile

[c]N—Normal weight; T—Thin (less than 10th percentile); O—Obese

[d]The term "epiphyseodesis" refers to physiological closure.

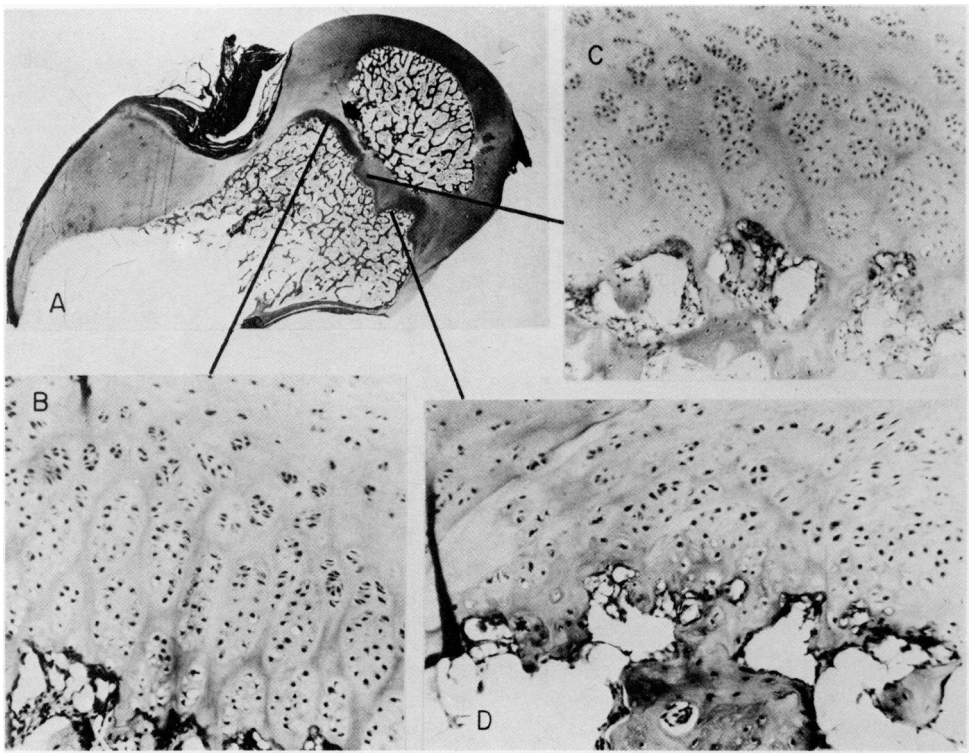

FIG. 5. A. Mid-coronal section of the proximal femur from a three-year-old girl with panhypopituitarism (4 X, Safranin 0). Note the well formed epiphyseal ossification center, and intense staining of the normal region of the physis, relative to the other regions of the physis. B. Regular cell column formation in the normal region of the physis (40 X, H and E). C. A region of abnormal physis, showing loss of cell columns, spherical (rather than longitudinal) enlargements of the cartilage clones, and increased intercellular matrix (40 X, H and E). D. Another region of abnormal physis, with greater cellular disarray, lack of both longitudinal or spherical cloning (as seen in 5B and 5C), and increased intercellular matrix (40 X, H and E).

volume (Figs. 5B–5D). While this child was much younger than the adolescents comprising the rest of this study, the cellular disarray in the physis due to the severe hypothyroidism and hypoadrenalism suggests a similar mechanism in the older affected child might predispose the capital femoral physis to slipping.

DISCUSSION

Undoubtedly the etiology of slipped capital femoral epiphysis is multifactorial, with the anatomic change (slip) representing the final common response of the capital femoral epiphysis to the predisposing factor(s). It may not be necessary for all the potential factors to be present for the slip to occur. Certain generalized disease states associated with physeal growth abnormalities (e.g., rickets), may be associated with multiple slipped epiphyses [29]. The mechanical factor of decreased resistance to shear stress across the hip joint may be implicated [26,30]. The adolescent period is also a time of significant histological change along the femoral neck, with the disappearance of functioning growth cartilage and perichondrium in this region, such that the greater trochanteric and capital femoral epiphyses and physes are no longer in cartilaginous continuity [31,32].

Since the affected age group is undergoing significant endocrine change and rapid growth, the possibility of endocrine irregularity as a predisposing cause has been

raised. Burrows [1] conducted an extensive study of one hundred cases of slipped capital femoral epiphysis and found that urinary ketosteroid excretion was normal. However, on the basis of other indications (notably, clinical appearance), he hypothesized that one-quarter of the boys and two-thirds of the girls suffered mild endocrine disturbance. Razzano [9], in a more detailed biochemical study of five patients, found normal levels of serum growth hormone and urinary estrogens and ketosteroids (this included assays in one patient during the acute phase). Thus, it would appear that the majority of patients have normal or relatively normal endocrine balance.

In contrast to the aforementioned data, an increasing number of patients with concomitant endocrinopathy and slipped capital femoral epiphysis have been described. Moore [17] reported a mentally retarded, hypogonadal twenty-one year old male. Lofgren [4] studied sixteen patients with the specific intent of discovering endocrine dysfunction; only two patients were involved (one had acromegaly, one had a craniopharyngioma). Sørenson [21] studied one hundred and one cases and found four unusual patients: three had hypopituitarism and one had ovarian dysgenesis. Primiano and Hughston [19] described a patient with hypogonadal, mosaic (XY/XXY) Klinefelter's syndrome. Müller [18] described multiple epiphyseal slips in a patient with coexistent pituitary and parathyroid tumors. Ehrengut [11] reported a patient with gynecomastia and failure of spermatogenesis. Farrow [12] reported a twenty-six year old male who had sustained a head injury at age eleven years with resultant chronic subdural hematoma and Simmond's disease. Strunz [22] reported a fifty-one year old male with panhypopituitarism. Semple and Goldschmidt [7] described a hypopituitary dwarf. Wouters [23] described three patients and Tissink [33] four patients with craniopharyngioma. Robin [20] reported a patient with acromegaly and slipped proximal humeral epiphysis with apparently undisplaced capital femoral epiphyses. Lovejoy and Lovell [16] described two cases with adiposogenital habitus, slipped capital femoral epiphysis and tibia vara (one ipsilateral, one contralateral). Kosowicz [14] reported similar medial tibial condylar involvement in nineteen patients with gonadal dysgenesis (Turner's syndrome), but found only irregularity of the capital femoral epiphysis, rather than slipping. Lewin [15] and Benjamin and Miller [10] described slipped capital femoral epiphysis in association with hypothyroidism (cretinism). Chiroff [34] described a child with primary hyperparathyroidism secondary to an adenoma. Two recent reports have documented slipped capital femoral epiphysis as a complication of treatment with growth hormone [2,6]. Interestingly, while one of the major arguments for endocrinopathic predisposition has been bilateral involvement, many of the aforementioned cases were unilateral.

The current concept is that the separation in slipped capital femoral epiphysis occurs between the zones of hypertrophy and provisional ossification, although the plane of separation is by no means confined to this region, but may extend toward the germinal zone or into the metaphysis. This results because of the irregularity of the contour of the physis in the slip-susceptible age range (Ogden, unpublished observations). The function of the hypertrophic zone is progressive elaboration of intercellular matrix and subsequent calcification of the matrix as a prelude to ossification [35]. In analyzing the potential role of endocrine dysfunction in the etiology of slipped capital femoral epiphysis, the effect of the various implicated hormones on the physis, and particularly the zone of hypertrophy, must be assessed.

The function of thyroxine in both prenatal and postnatal differentiation and growth of the various skeletal components is incompletely understood. Adams and

co-workers [36,37] showed that appropriately timed administration of thiourea to incubating chicken embryos caused inhibition of general body growth and selective tibial shortening. Other investigators found that thyroxine caused initial enhancement of cartilage maturation, followed by retardation of bone growth [38], and that the tibia and radius were particularly affected by growth retardation [39]. Melcher [40] demonstrated that thyroxine induces DNA synthesis in the hypertrophic chondrocytes of Meckel's cartilage, while others have shown a generalized enhanced cartilage formation due to thyroxine [41,42]. Thyroxine can induce the differentiation of non-cartilage-making chondrocyte clones into functional cells that will produce chondroitin sulfate [43].

Skeletal growth appears to be more affected than other organ systems in hypothyroid embryos because (a) all constituent skeletal cells appear to be especially dependent upon thyroxine, and (b) the formation of large amounts of collagen and acid mucopolysaccharides is closely regulated by circulating levels of thyroxine [44–46]. Dziewiatkowski [47] demonstrated that sulfated acid mucopolysaccharides of the cartilage matrix were very sensitive to circulating thyroxine. This thyroxine-induced chondrogenesis includes enhanced physeal cartilage maturation and its subsequent replacement by bone [48–50]. In contrast, both hypothyroidism in rats and cretinism in humans are associated with persistent, matrix-deficient epiphyseal cartilage and delayed formation of the secondary ossification center within the epiphysis [46,49,51]. Further, in experimental hypothyroidism the incorporation of amino acids into the basic protein sequential structure of collagen may also be abnormal [52,53].

Hall [45] studied thiourea treated chick embryos (i.e., chemically hypothyroid) and showed (a) a loss of integrity of the articular cartilage, (b) extensive erosion of the hyaline and articular cartilage, (c) excessive vascularization of the epiphyses, (d) abnormal distribution of the matriceal acid mucopolysaccharides, and (e) no effect upon osteogenesis per se. These findings strongly suggest a prominent role of thyroxine in the normal maintenance of cartilage integrity, control of the rates of erosion and resorption of the cartilage model, and an integral role in the synthesis or deposition of acid mucopolysaccharide-protein complexes in the epiphyseal and physeal matrices. Thyroxine deficiency can therefore be expected to cause some loss of structural integrity in the zone of hypertrophy of the physis.

The effect of thyroxine on normal skeletal growth and maturation appears to be functionally interrelated with growth hormone (somatotrophin). The administration of thyroxine to thyroidectomized/hypophysectomized rats caused significant skeletal maturation but only moderate overall skeletal growth, whereas administration of growth hormone to similar animals produced increased body weight and skeletal dimensions, but had minimal effect on skeletal maturation. However, the administration of both hormones restored both growth and maturation to the developing skeleton [54].

Growth hormone appears to influence skeletal growth by affecting the cells of the resting/germinal zones of the physis, and the corresponding cell zones around the developing epiphyseal ossification center. However, the actual mode of action, whether direct or indirect, has not yet been completely clarified. Evidence seems to support a second hormone, somatomedin or sulfation factor, as the active component on the skeletal system. Those studies that have attempted to find abnormal growth hormone levels in slipped capital femoral epiphysis may have failed for two important reasons. First, sequential graphic analyses of growth hormone have demonstrated that the differences between adults and children lie not in continuously elevated secretion, but rather much higher and more frequent secretion peaks during

each twenty-four hour period in children. This finding alone emphasizes the futility of attempting to estimate growth hormone levels from single random samples. Second, in a study of growth patterns before and after surgical removal of craniopharyngiomas, Holmes [55] suggested that there might be a primary growth determinant, such as insulin or sulfation factor, other than what can be measured by direct growth hormone radioimmunoassay, or that levels of growth hormone much lower than those usually considered significant may be capable of supporting normal skeletal growth. Morscher [26,27] found that growth hormone did not alter the basic qualitative strength of the physis to tensile stress separation, while Harris [3] showed that growth hormone caused a decreased resistance of the physis to shear stress.

Seinsheimer and Sledge [56] tested the response of various rat physes to somatomedin (sulfation factor) and suggested that growth rates in the physes were controlled by (a) modulating the cell cycle time of the proliferating zone of chondrocytes, and (b) adjusting the rate of synthesis of matrix by the chondrocytes in the hypertrophic zone.

A related potential cause of slipped capital femoral epiphysis is the possibility of a hypothalamic hormone capable of inhibiting the release of growth hormone. Such a chemical, somatostatin, has now been isolated from the rat brain [57]. However, as will be shown, there also appears to be a certain degree of suppression of the end organ (peripheral) effects of growth hormone by certain gonadotrophins.

While the absolute tensile strength of the physis increases with the increasing cross-sectional area that results from growth, the qualitative resistance (per unit area) to traction forces increases with age only until the onset of puberty. At this time period of beginning sexual maturity in rats, the progressive increase in the tensile strength slows down, and there is even a decrease in the qualitative strength per unit area in male rats (but not in female or castrated male rats) [27].

It has been demonstrated that the effect of androgens is always a composite of two opposite effects: the anabolic and the androgenic. During sexual maturation the anabolic effect of the androgens prevails, whereas for estrogens a strong maturation promoting effect always dominates. The anabolic effect of testosterone may be responsible for the more rapid growth of male rats and also for the weakening of the physis at pubescence. Only with higher concentrations and longer duration does the androgenic effect prevail. This androgenic effect causes narrowing of the physis, slowing down of the speed of growth and mechanical consolidation of the cartilage [26,27].

Exogenous or endogenous androgens may also function as a potent stimulus facilitating growth hormone release in some males with delayed secondary sexual development. However, the stimulatory function is evident only in the presence of an intact pituitary [58]. Since many patients with slipped capital femoral epiphysis exhibit the "Frohlich" habitus, it is possible these children may have wider fluctuation of growth hormone levels, with an erratic effect on normal physeal growth rates.

In contrast pharmacologic doses of estrogens caused a partial inhibitory effect upon growth hormone-induced widening of the tibial physis in hypophysectomized rats, suggesting that the estrogenic steroids were capable of suppressing certain peripheral somatotrophic effects [59]. Such an effect has also been demonstrated recently in humans [60]. Further, work has shown that the estrogens may specifically suppress sulfation factor functions [61].

Histologically, at the onset of sexual maturation, the ratio of the width of the resting/germinal/dividing zones to the hypertrophic zone shifts in favor of the latter. This leads to greater intercellular volume of calcifying cartilage, which increases the amount of the potentially weak layer of the zone of hypertrophy. When this layer is

closing at physeal maturity, there is a marked slowing of longitudinal growth, a decreased thickness of all physeal zones, and a rapid increase in cartilage strength. These processes certainly appear facilitated by estrogens, but blocked by androgens, either directly, or indirectly, by the effect of somatotrophin or somatomedin (sulfation factor).

The potential mechanisms for these differing effects of sex hormones on the physis may be found at the ultrastructural/biochemical level. Estrogen administration caused increased intracellular secretory activity in the zone of matrix formation, particularly with regard to intracellular formation of protein-polysaccharide complexes; however, these were not released, and thereby caused increased intracellular polymerization of precollagenous products and accelerated cellular hypertrophy and maturation [62]. In contrast, testosterone caused increased intracellular deposition of glycogen and lipids and an increased discharge of protein-polysaccharide complexes into the extracellular matrix, without affecting intracellular collagen metabolism [62]. These changes that were observed at the ultrastructural level may relate to direct biochemical effects, for it has been shown that estrogen (estradiol) selectively increases the activity of three glucocorticoid-inducible enzymes—tryptophan oxygenase, tyrosine aminotransferase and alanine aminotransferase—concerned specifically with amino acid metabolism (i.e., matrix formation) [63]. In the same study it was demonstrated that androgens suppressed the response of at least tryptophan oxygenase to estrogens. These enzyme-hormone interactions might cause the aforementioned protein-polysaccharide differences in the zone of hypertrophy.

Estrogen may also enhance calcium deposition in both bone and calcifying regions of the zone of hypertrophy. A characteristic change during normal epiphyseal union is increased mineralization and multiple tide lines on both the epiphyseal and metaphyseal sides of the physis (Ogden, unpublished data). This increased calcification may also increase the stability of the zone of hypertrophy.

Shea and Mankin [29], in analyzing the relationship of chronic renal disease and slipped epiphyses, speculated that the lesions of the epiphyseal plate were due either to a defect in the protein matrix synthesis or to excessive parathyroid hormone.

While the potential for avascular necrosis as a post-operative complication is widely discussed, the possibility of vascular ischemia as one of the antecedents to slipped capital femoral epiphysis is rarely suggested. Moore [17] described a previously untreated twelve year old boy who underwent resection of a portion of the femoral head for degenerative joint changes secondary to slipped capital femoral epiphysis; the pathology showed necrotic areas of bone with partial replacement by new bone, quite similar to the creeping substitution described in adult avascular necrosis. The pathologic changes described by Howorth [28] and Ponseti and McClintock [5] show changes that are similar to the experimental changes described by Trueta [64] for epiphyseal and metaphyseal ischemia. Crawford [65] has recently described a seven year old boy with Legg-Perthes disease who sustained a contralateral slipped capital femoral epiphysis one year after institution of abduction brace treatment. Spivey and Park [66] subjected immature rabbits to repeated ischemic episodes and produced several slipped capital femoral epiphyses, with histologic changes similar to those described in the human.

Ischemic changes leading to epiphyseal damage and physeal irregularity have been described in experimental scoliosis secondary to lathyrism [67]. Ponseti and coworkers [68,69] showed that rats fed diets containing aminonitriles develop skeletal changes characterized by severe growth plate cellular disarray, and suggested that a similar biochemically-induced structural change might also exist in slipped capital femoral epiphysis. Subsequently it was shown that semicarbazide compounds could

also produce irregularities in the physes, with these changes being most prominent in the long bones [70]. The characteristics of these compounds are vascular irregularity and abnormal widening of the hypertrophic zone, with failure to progress to calcification and ossification. In contrast, another compound, mercaptophthylamine, which causes similar gross epiphyseal slipping and structural abnormality, causes preferential enlargement in the zone of proliferating cartilage [70].

The biochemical disruption common to all these compounds is a decreased polymerization of the ground substance (intercellular matrix). Leonard [71] showed that the lathyrogenic compound beta-amino proprionitrile (BAPN) does not affect previously cross-linked collagen, but does permanently impair the ability of newly synthesized collagen to form cross-linkages. BAPN blocks the primary conversion of lysyl residues of tropocollagen to the peptide-bound allysine [72]. Penicillamine will block the final linkage condensation steps between two allysyl residues [73]. Both compounds, by affecting collagen cross-linkage, produce increased amounts of neutral salt soluble collagen. BAPN does not alter either the biosynthesis of tropocollagen or degradation of preformed or insoluble collagen. Bone and cartilage appear to have a high degree of cross-linking. The rapid introduction of such cross-linkage undoubtedly provides needed stabilization of bone collagen prior to and during the process of mineralization [74]. Mills and Bavetta [75] have demonstrated that maturation and increased cross-linkage of newly synthesized collagen precedes calcification, and that calcium binding to the salt soluble fractions occurs during the earliest stages of polymerization. Henneman [76] showed that the lathyrogenic effects of BAPN on both skin and bone collagen may be inhibited by the administration of estrogenic compounds. These estrogenic compounds may accelerate polymerization and facilitate calcium binding, thereby stabilizing the newly synthesized collagen and increasing cartilage stability and tensile strength.

While the aforementioned discussion centered around experimental situations induced by chemicals not normally ingested by man, the selective effect on the hypertropic region, the slipping of multiple epiphyses, and the stabilization and even reversal of the effects by estrogens, makes this model a reasonable one for further study of slipped capital femoral epiphysis. In particular, studies such as those done by Henneman [76] might be repeated using androgenic compounds, somatotrophin and somatomedin.

An important finding in the current study, which has not been described in the previous reports in the literature, is delay in closure of the capital femoral physis. In general epiphyseodesis occurs within two to three months following bone pegging (Howorth [28] procedure), while nine to twelve months will usually lapse if the patient is treated with Knowles pinning. In sharp contrast case 1 took 24 and 36 months, case 2 took 4½ and 5½ years and case 3 took 15 months to epiphyseodese. Only case 3 evinced closure within a year. Furthermore, case 1 exhibited elongation of the femoral neck, despite the use of threaded pins, and "outgrew" the pins on one side. Because of these findings, we recommend the use of Knowles pins for stability, and concomitant extra-articular bone graft (Bonfiglio procedure) to enhance the rate of epiphyseodesis.

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